БІОТЕХНОЛОГІЇ ТА БІОІНЖЕНЕРІЯ

UDC 573.6:546.23:547.972.3

Bionanotechnological strategies for the synthesis of quercetin conjugates with selenium nanoparticles for their targeting of the Wnt/Ca2+signaling pathway

Bityutskyy V.S.[1], Tsekhmistrenko S.I.[1], Demchenko O.A.[2], Tsekhmistrenko O.S.[1], Melnychenko Yu.O.[1], Kharchyshyn, V.M.[1]

[1] *BilaTserkva National Agrarian University*
[2] *D.K. Zabolotny Institute of Microbiology and Virology of the National Academy of Sciences of Ukraine*

Bityutskyy V.S. E-mail: Voseb@ukr.net

Бітюцький В.С., Цехмістренко С.І., Демченко О.А., Цехмістренко О.С., Мельниченко Ю.О., Харчишин В.М. Біонанотехнологічні стратегії синтезу кон'югатів кверцетину з наночастинками селену з метою їх націлювання на сигнальний шлях Wnt/Ca2+. Збірник наукових праць «Технологія виробництва і переробки продукції тваринництва», 2023. № 2. С. 100–107.

Bityutskyy V., Tsekhmistrenko S., Demchenko O., Tsekhmistrenko O., Melnychenko Yu., Kharchyshyn V. Bionanotechnological strategies for the synthesis of quercetin conjugates with selenium nanoparticles for their targeting of the Wnt/Ca2+signaling pathway. «Animal Husbandry Products Production and Processing», 2023. № 2. PP. 100–107.

Рукопис отримано: 13.09.2023 р.
Прийнято: 27.09.2023 р.
Затверджено до друку: 23.11.2023 р.

doi: 10.33245/2310-9289-2023-182-2-100-107

One of the applications of nanotechnology is the synthesis of nanoparticles for targeted drug delivery and disease prevention. In the agricultural sector, nanotechnology holds great promise for improving animal health and productivity. The article discusses the advantages of «green» synthesis of selenium nanoparticles functionalized with the flavonoid quercetin and their potential in the prevention of bone diseases in broilers. Selenium is an important trace element that plays a crucial role in various physiological processes, including the regulation of bone metabolism. Its deficiency can lead to bone diseases such as osteoporosis and osteomalacia. On the other hand, quercetin, a naturally occurring plant compound, has been shown to have numerous health benefits, including anti-inflammatory, antioxidant, and anticancer properties. However, quercetin's bioavailability and stability are limited, making its therapeutic potential challenging to exploit. To overcome these limitations, we have developed bionanotechnological strategies for the synthesis of quercetin conjugates with selenium nanoparticles. This approach not only improves the stability and bioavailability of quercetin, but also allows for targeted delivery to specific tissues or cellular pathways. Functionalization of Selenium nanoparticles with the flavonoid quercetin promotes the effect of the nanoconjugate on the transcription factors Nrf2 and NF-kB, Wnt, key pathways that regulate the delicate balance of cellular redox status and responses to stress and inflammation, calcium and phosphorus metabolism. In this case, the target is the Wnt signaling pathway, a complex cascade of processes involved in bone metabolism. It has been found that the synthesized nanoselenium-quercetin bioconjugates modulate the Wnt signaling pathway in different ways. Firstly, they reduce the activity of the protein β-catenin, a key regulator of the Wnt signaling pathway, and help maintain a balance between bone formation and resorption, thus preventing bone disease. Secondly, these bioconjugates increase the activity of LRP6, a Wnt receptor protein, which further enhances the effectiveness of the signaling pathway. Finally, they affect the expression of genes activated by the Wnt signaling pathway, thus regulating the metabolism of calcium and phosphorus, important elements for bone health. The potential of these bionanotechnology strategies is enormous, especially in the agricultural sector. By preventing bone disease in broilers, disease prevention and poultry productivity can be significantly increased. The use of nanotechnology advances can serve as an environmentally friendly alternative to the use of antibiotics and other pharmaceuticals, contributing to the overall health and well-being of animals. Thus, the «green» synthesis of quercetin-functionalized selenium nanoparticles offers a promising solution for targeting the Wnt signaling pathway, regulating calcium and phosphorus metabolism, and preventing bone disease in broilers. This bionanotechnology approach not only improves the stability and bioavailability of quercetin, but also enhances its therapeutic potential. By harnessing the potential of nanotechnology in the agricultural sector, we can improve animal health, reduce disease and increase productivity, ultimately benefiting both animals and humans.

Key words: bionanotechnology, «green» synthesis, Nrf2 factor, NF-kB, Wnt, β-catenin, Selenium, Calcium, Phosphorus.

"Green" synthesis. Nanotechnology has revolutionised various sectors, including electronics, energy, biology, medicine, and agriculture. Its integration with biology, which has led to bionanotechnology, has opened up new horizons in healthcare, diagnostics and drug delivery systems. Bionanotechnology is used to develop biosynthetic and environmentally friendly technologies for the synthesis of nanomaterials, with green synthesis and surface modification of nanoparticles being crucial [15; 23].

Nanoparticles synthesized using plant extracts or phytocomponents are of great importance in the development of various therapeutic and diagnostic agents [1]. "Green synthesis is an environmentally friendly alternative to traditional synthesis methods and aims to avoid or minimize toxic components used in physicochemical methods and can successfully compete with them in terms of speed, controllability, bioconversion and reduction of the cost of the final product [24]. The production of nanoparticles using biological material has a number of advantages: low cost of raw materials, low toxicity, short production time, safety, ability to regulate the required volume of products, and suitability for large-scale production [6].

The need for alternative methods of protecting organisms, improving the quality of products, and creating a national economy can be met by nanotechnology [11].

Biotechnology in poultry farming. The poultry industry has to solve a number of problems. A common bone disease in fast-growing poultry worldwide is tibial dyschondroplasia. Annual losses in the meat poultry industry from musculoskeletal diseases are 2–6%, which reaches 40–60% of the total number of musculoskeletal diseases. Chronic mild intestinal inflammation negatively affects poultry performance and impairs nutrient absorption. Gut permeability is controlled by the intestinal microbiota, digestive secretions, physical barriers and chemicals such as cytokines. Treatable strategies aimed at regulating the gut microbiota can control several diseases closely related to inflammatory and metabolic disorders. Observations in Europe have shown that the poultry industry has faced a number of challenges following the ban on growth promoter antibiotics, including negative impacts on productivity, animal welfare and general health issues. Today, alternatives to antibiotics such as probiotics, prebiotics and botanicals are increasingly being used. Chicken enteritis is a complex intestinal disease caused by bacteria, viruses, parasites and various regulatory factors. Certain flavonoids, such as quercetin, naringin and luteolin, have been found to relieve intestinal inflammation. The ability of flavonoids to inhibit the transcription factor NF-κB is one of the most promising approaches to explaining the mechanism of anti-inflammatory action of these plant polyphenols. It is also worth noting the possible role of isoflavones in the development of inflammation of the Keap1/Nrf2/ARE signalling system, which controls the state of internal homeostasis by regulating various stages of cell proliferation, differentiation and apoptosis. Quercetin is a natural flavonoid that neutralizes free radicals and has antioxidant, antitumour, and anti-inflammatory effects [2]. Quercetin suppresses the expression of TNF-α, IL-1β, IL-6 and GM-CSF(granulocyte-macrophagecolony-stimulatingfactor)in macrophages induced by lipopolysaccharides, improves calcium absorption in the small intestine and increases the activity of the vitamin D receptor.

The flavonoid quercetin has been shown to counteract inflammatory processes by activating the Nrf2/HO-1 signalling pathway and inhibiting NF-kB signalling, regulating neuronal excitability and NMDARs(*N*-methyl-D-aspartatereceptors**)** trafficking [16]. Quercetin supplementation improved calcium and phosphorus metabolism and promoted tibia development, preventing foot disease in broilers through the Wnt signalling pathway [13]. However, the use of this flavonoid is limited by its low absorption in the body due to its poor solubility, permeability, instability and bioavailability [3].

It has been proven that various strategies and biomodifiers are used for surface modifications/functionalization of nanomaterials, including flavonoids [8]. In particular, the functionalization of Selenium nanoparticles with quercetin can contribute to the effect of the nanocomposite on the transcription factors Nrf2 and NF-kB, Wnt, key pathways that regulate the delicate balance of cellular redox status and responses to stress and inflammation, calcium and phosphorus metabolism [2; 7; 25].

The Wnt signalling pathway plays a key role in embryonic development, cell proliferation and differentiation, and dysregulation of signal transduction. Wnt can lead to neoplastic transformation in various organ systems [17]. Wnt ligands (19 members in mammals) are secreted proteins that activate various intracellular signal transduction pathways and regulate tissue growth and renewal. Since the identification of the first member in 1982, the Wnt signalling pathway has attracted considerable attention of scientists, as it is essential for embryonic development, adult tissue homeostasis and regeneration, and dysregulation of Wnt can lead to many pathologies, including tumour-like development [14].

The name Wnt is a hybrid word created from the names Wingless and Int-1, and is derived from integrase-1 (Int-1) in mouse breast cancer combined with the Drosophila gene wingless (suppresses wing development in flies), as the two genes are functionally similar [19].

Wingless/integrase-1 belongs to the family of cysteine-rich glycoprotein growth factors encoded by Wnt genes, which are highly conserved among vertebrate species [12]. Wnt consists of a canonical and a non-canonical signal transduction pathway, which can be divided into two branches: Wnt/PCP – the Planar Cell Polarity pathway, which is responsible for the correct polarization of cells during tissue formation, and Wnt-cGMP – the cyclic guanosine monophosphate/Ca^{2+}pathway [28]. The canonical pathway (Fig. 1), the most well-known branch, is activated when Wnt binds to its receptors, which leads to stabilization of cytoplasmic β-catenin and activation of Wnt-regulated genes.

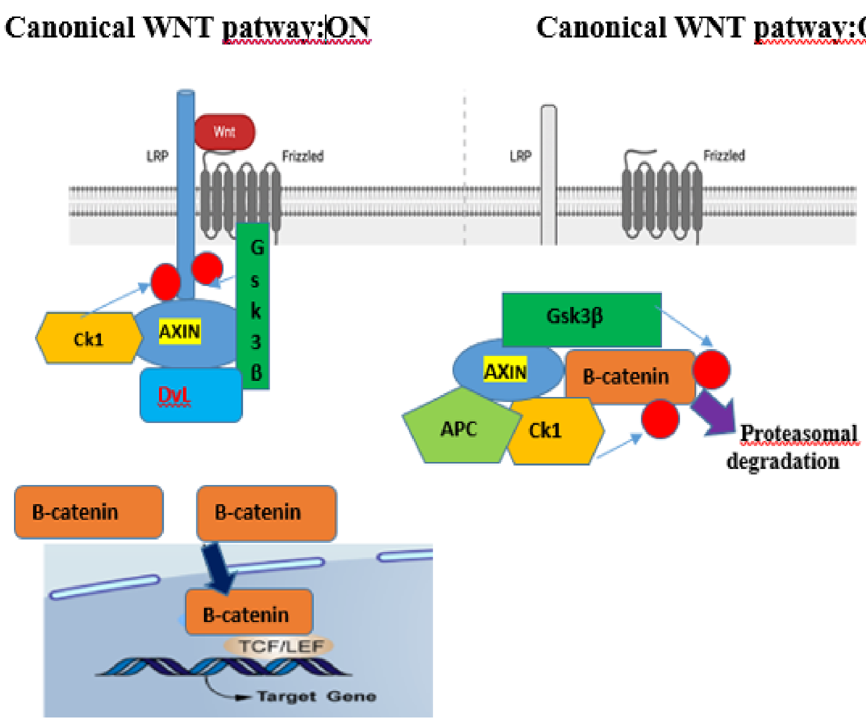

Fig. 1. **Thecanonical Wnt/ß-cateninpathwayis ON:** when a Wnt ligandbindstotheLRP5/6 and Fz receptors, the scaffolding protein Disheveled (Dvl) recruits Axin1 and the kinases CK1 and GSK3ß to the membrane, disrupting the degradation complex and disrupting ß-catenin phosphorylation and degradation. ß-catenin accumulates in the cytoplasm and subsequently moves to the nucleus, where it acts as an activator of TCF/LEF-mediated transcription of target Wnt genes. The canonical Wnt/ß-catenin pathway is OFF (OF): in the absence of Wnt binding to Frizzled (Fz) receptors and LRP5/6 coreceptors, ß-catenin interacts with the degradation complex (CK1, GSK3β, Axin1 and APC), which leads to its phosphorylation by GSK3ß and CK1 and its subsequent degradation by the proteasome. CK1, casein kinase 1; GSK3ß, glycogen synthase kinase 3β; Axin1, axis inhibition protein 1; APC, adenomatous polyposis coli; Tcf, T-cell factor; LEF, lymphocyte binding factor; Rock, Rho-related protein kinase 1 containing helix; RhoA, RAS homologue member of the A gene family; JNK, Jun N-terminal kinase.

Wnt/β-catenin signalling is a highly complex pathway that plays different roles in different cellular processes. Although Wnt ligands typically transmit signals through their specialised Frizzled receptors, the decision to use a β-catenin-dependent or β-catenin-independent signalling pathway depends on the type of co-receptor used. Classical Wnt signalling is dependent on β-catenin, whereas non-classical Wnt signalling, by traditional definition, is not, although current evidence suggests that both pathways interact with intertwined networks involving the use of different ligands, receptors and co-receptors. β-catenin can be directly phosphorylated by several kinases that control their participation in typical and atypical pathways. In addition, cofactors associated with β-catenin determine the outcome of this pathway in terms of genes that induce proliferation or promote differentiation. Thus, protein phosphorylation controls WNT/β-catenin signalling, in particular in cancer processes [21; 29].

Glycogen synthase kinase 3β (GSK3β) and casein kinase 1 (CK1) promote β-catenin phosphorylation in the degradation complex, enhancing its ubiquitination and leading to subsequent proteasomal degradation.

Regulation of the Wnt signalling pathway. Calcium and phosphorus play an important role in the Wnt signalling pathway, in particular in the Wnt/Ca^{2+}pathway [5; 9; 12].

The Wnt/Ca^{2+}pathway is initiated by Frizzled receptors, which activate the classical G-protein-coupled signalling pathway. Frizzled G protein signalling activates phospholipase C-beta (PLC-beta), which cleaves phosphatidylinositol 4,5-bisphosphate (PIP2) into 1,2-diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3) [18]. The Wnt/Ca^{2+}pathway can counteract the canonical Wnt pathway, but it is unclear whether this pathway is conserved in mammals and whether it is involved in tumour formation [9]. Signalling through frizzled-G protein activates the Wnt/Ca^{2+}pathway, which leads to a short-term increase in the level of free calcium in the cytoplasm, which subsequently activates the following effectors.

An analysis of these processes and connections, which are covered by the Kyoto Encyclopedia of Genes and Genomes (KEGG), indicates that this pathway is also linked to calcium and phosphorus metabolism and the flavonoid quercetin [10].

Quercetin, a flavonoid found in various fruits and vegetables, has been shown to regulate calcium and phosphorus metabolism through the Wnt signalling pathway in broilers [26]. Studies have shown that flavonoids can affect key regulators of calcium and phosphorus metabolism in this pathway [2]. In addition, quercetin has been shown to inhibit angiotensin II-induced vascular smooth muscle cell proliferation and activation of the JAK2/STAT3 pathway [4; 27]. The KEGG pathway assessment showed that quercetin affects various signalling pathways, including the PI3K-AKT signalling pathway, cytokine receptor-cytokine interaction, JAK-STAT signalling pathway, MAPK signalling pathway, and cancer pathways [27].

Interestingly, the Wnt/β-catenin signalling pathway is also involved in the biosynthesis of phenylpropanoids/flavonoids, suggesting a potential role for the Wnt signalling pathway in the regulation of flavonoid biosynthesis, including quercetin. This highlights the complex interplay between the Wnt signalling pathway, calcium and phosphorus metabolism, and quercetin.

The Wnt/Ca^{2+}pathway, a branch of the Wnt signalling pathway, plays a crucial role in this regulation [10]. This pathway uses G-proteins and phospholipases to induce a temporary increase in cytoplasmic calcium levels, subsequently activating downstream signalling pathways. For example, Wnt4 can activate the calcium signalling pathway via cAMP in maturing β cells, controlling calcium signalling, metabolism and function. In broilers, quercetin has been shown to regulate calcium and phosphorus metabolism through the Wnt signalling pathway. Although the precise mechanism remains unclear, it is suggested that flavonoids such as quercetin affect key regulators of calcium and phosphorus metabolism in the Wnt signalling pathway.

Frizzled receptors can trigger both β-catenin-dependent and β-catenin-independent signalling, among which the Ca2+ pathway has been studied in detail. Thus, in the Wnt/Ca^{2+} pathway, Wnt-Ca^{2+}signalling is mediated through G-proteins and phospholipases and causes a temporary increase in free calcium in the cytoplasm, which subsequently activates the following effectors [10]. Accordingly, quercetin is able to affect key regulators of calcium and phosphorus metabolism in the Wnt signalling pathway, and this effect can be mediated through the Wnt/Ca^{2+} pathway (Fig. 2).

Quercetin has been shown to inhibit β-catenin-dependent transcriptional activity, which is a critical step in the activation of the Wnt/β-catenin pathway. It also inhibits uPAR((urokinase-type plasminogen activator receptor)-mediated activation of this pathway. Studies have shown its effects on different components of the pathway in different types of cancer cells, leading to growth inhibition. When it interacts with β-catenin, quercetin blocks the binding between β-catenin and Tcf, which leads to inhibition of the growth of cancer cells, such as mouse 4T1 breast cancer cells [19].

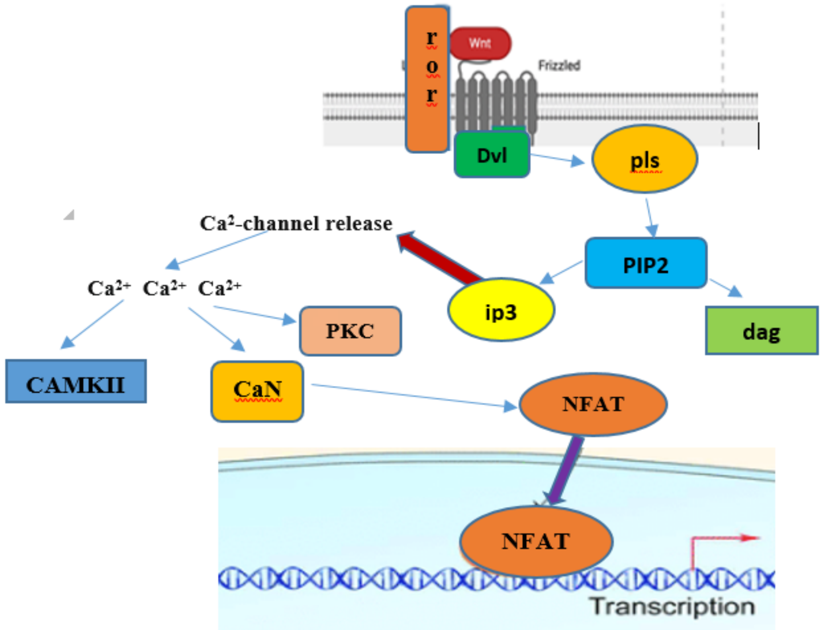

Fig. 2. **The β-catenin-independent Wnt/Ca^{2+} pathway.** In the Wnt/Ca^{2+} pathway, Wnt ligands transmit signals through Frizzled (Fzd) and tyrosine kinase-like orphan receptor 1/2 (ROR1/2) coreceptor receptors to induce Dvl-dependent cleavage of phosphatidylinositol 4,5-bisphosphate by phospholipase C (PLC) (PIP2), producing inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 acts on Ca^{2+} channels in the endoplasmic reticulum, leading to a cytosolic Ca^{2+}wave that drives the activity of protein kinase C (PKC) and Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII). CaN dephosphorylates NFAT, which leads to its nuclear translocation and expression of NFAT target genes [adapted from 20].

In SW480 colon cancer cells, quercetin was found to inhibit the transcriptional activity of β-catenin/Tcf. In addition, it reduces the levels of β-catenin and the Tcf-4 product in the nucleus, which further prevents the activation of the Wnt/β-catenin pathway [21].

In summary, the Wnt signalling pathway, calcium and phosphorus metabolism, and the flavonoid quercetin are closely related. The Wnt signalling pathway regulates calcium and phosphorus metabolism through the Wnt/Ca^{2+}pathway, and quercetin has been shown to modulate this pathway. In addition, quercetin inhibits the nuclear translocation of β-catenin.

Calcium and phosphorus play an important role in the Wnt signalling pathway, which is involved in embryonic development, cancer, and normal physiological processes in adults [29]. The Wnt signalling pathway is closely related to calcium and phosphorus metabolism, and studies have shown that flavonoids can affect key regulators of calcium and phosphorus metabolism in the Wnt signalling pathway. The main DEGs (differentially expressed genes) in the Wnt signalling pathway that regulate calcium and phosphorus uptake and metabolism include Wnt-5a, calcium/calmodulin-dependent protein kinase II (CAMK2G, CAMK2D, CAMK2B), phospholipase C, beta 4 (PLCB4), protein kinase C alpha (PRKCA) and nuclear factor of activated T cells-1 (NFATC1) [26]. Calcium and phosphate homeostasis is regulated by several hormones, including PTH, vitamin D, FGF23 and calcitonin, and is critical for proper bone formation and maintenance. Calcium and phosphorus transport is regulated by PTH and FGF23 in the kidneys, and by PTH and calcitonin in bones [22]. The Wnt signalling pathway regulates calcium release from the endoplasmic reticulum (ER) to control intracellular calcium levels. In general, calcium and phosphorus play a role in the Wnt signalling pathway by regulating the metabolism and absorption of calcium and phosphorus, which are critical for proper bone formation and maintenance.

Wnt proteins are secreted morphogens that are essential for basic developmental processes, such as cell specification, proliferation of progenitor cells and control of asymmetric cell division, in many different species and organs. There are at least three distinct Wnt pathways: the canonical pathway, the planar cell polarity (PCP) pathway, and the Wnt/Ca^{2+}pathway. In the canonical Wnt pathway, the main effect of Wnt ligand binding to the receptor is to stabilize cytoplasmic β-catenin by inhibiting the β-catenin degradation complex. After that, β-catenin can freely enter the nucleus and activate Wnt-regulated genes through interaction with Tcf (T-cell factor) transcription factors and the concomitant recruitment of co-activators. Planar cell polarity (PCP) signalling leads to the activation of small GTPases RHOA (RAS homologue gene-family member A) and RAC1, which activate the stress kinases JNK (Jun N-terminal kinase) and ROCK (RHO-associated coiled-coil-containing protein kinase 1), resulting in cytoskeletal remodelling, changes in cell adhesion and motility. WNT-Ca2+ signalling is mediated through G proteins and phospholipases and leads to a temporary increase in the level of free calcium in the cytoplasm, which subsequently activates the kinases PKC (protein kinase C) and CAMKII (calcium-calmodulin-mediated kinase II), as well as the phosphatase calcineurin [10].

Conclusions. At present, it is important to solve the problem of increasing the effectiveness of natural phytonutrients, in particular the flavonoid quercetin, by conjugating it with nanoparticles. The chemical reactivity of flavonoids depends on their radical scavenging properties, which can reduce oxidative stress in cells. At the same time, certain flavonoids have strong anti-inflammatory capacity, which, together with its antioxidant activity, creates excellent opportunities, such as chemoprevention of oxidative stress and reduction of inflammation accompanying many pathologies. However, these compounds have low water solubility, chemical instability, rapid metabolism and poor bioavailability, which compromises their therapeutic efficacy. Therefore, new approaches are needed to take advantage of the beneficial effects of phytonutrients while expanding their potential use in the prevention of a number of disorders. In this context, nanoparticles are particularly interesting when used to deliver phytocomposites and enhance their bioavailability. In addition, the ability to be functionalized with specific ligands that target specific organs or cells is also very important, as it is possible to increase the concentration of the phytoconjugate at the desired target site while reducing side effects. Thus, the beneficial effects of phytonutrients can be further enhanced by nanotechnology, which will help improve the current use of these compounds with such great preventive and therapeutic potential. "Green” methods for the synthesis of nanoparticles with plant extracts are promising because they are simple, convenient, environmentally friendly and require shorter reaction times. The synthesizednanoselenium-quercetin bioconjugates can modulate the Wnt signalling pathway in various ways: by reducing the activity of the protein β-catenin, which is a key regulator of the Wnt signalling pathway; by increasing the activity of the protein LRP6, which is a Wnt receptor; by affecting the expression of genes activated by the Wnt signalling pathway. This cascade of complex processes regulates the metabolism of calcium and phosphorus, which contributes to the prevention of bone diseases, and can increase the potential of the agricultural sector to reduce diseases, improve the safety and productivity of animals and poultry.

REFERENCES

1. Adeyemi, J.O., Oriola, A.O., Onwudiwe, D.C., &Oyedeji, A.O. (2022). Plant extracts mediated metal-based nanoparticles: Synthesis and biological applications. Biomolecules, 12(5), 627 p. DOI:10.3390/biom12050627

2. Aoiadni, N., Ayadi, H., Jdidi, H., Naifar, M., Maalej, S., Makni, F.A., Koubaa, F.G. (2021). Flavonoid-rich fraction attenuates permethrin-induced toxicity by modulating ROS-mediated hepatic oxidative stress and mitochondrial dysfunction ex vivo and in vivo in rat. Environmental Science and Pollution Research, 28, pp. 9290–9312. DOI:10.1007/s11356-020-11250-9

3. Bityutskyy, V.S., Tsekhmistrenko, I.S., Melnychenko, Yu.O. Tsekhmistrenko, S.I. (2023). The Wnt signaling pathway, calcium and phosphorus metabolism and the regulatory role of the flavonoid quercetin. Technologies, tools and strategies for implementing scientific research, pp. 97–100 (in Ukrainian).

4. Bundy, K., Boone, J., Simpson, C.L. (2021). Wnt signaling in vascular calcification. Frontiers in Cardiovascular Medicine, 8, 708470. DOI:10.3389/fcvm. 2021.708470

5. De, A. (2011). Wnt/Ca^{2+} signaling pathway: a brief overview. Acta BiochimBiophys Sin, 43(10), pp. 745–756. DOI:10.1093/abbs/gmr079

6. Dejen, K.D., Sabir, F.K., Ananda Murthy, H.C., Ayanie, G.T., Shume, M.S., Bekele, E.T. (2023). Green Synthesis of Nanomaterials for Environmental Remediation. In Green Nanoremediation: Sustainable Management of Environmental Pollution. Cham: Springer International Publishing, pp. 27–65.

7. Demchenko, A., Bityutskyy, V., Tsekhmistrenko, S., Tsekhmistrenko, O., Kharchyshyn, V. (2022). Synthesis of functionalized selenium nanoparticles with the participation of flavonoids. Multidisciplinary academic notes. Theory, methodology and practice. In Proceedings of the XVII International Scientific and Practical Conference. Tokyo, Japan, pp. 29–35. DOI:10.46299/ISG.2022.1.17 (in Ukrainian)

8. Demchenko, A., Bityutskyy, V., Tsekhmistrenko, S., Melnichenko Yu., Kharchyshyn V. (2023). Effect of selenium nanoparticles obtained by the method of green synthesis with the participation of probiotics and flavonoids on metabolic and zootechnical parameters of broiler chickens. Modernization of today’s science: experience and trends: IV International Scientific and Theoretical Conference. Singapore, pp. 64–66.

9. Duchartre, Y., Kim, Y. M., & Kahn, M. (2016). The Wnt signaling pathway in cancer. Critical reviews in oncology/hematology, 99, pp. 141–149. DOI:10.1016/j.critrevonc.2015.12.005

10. KEGG Wnt signaling pathway – Homo sapiens (human). Available at:https://www.genome.jp/pathway/hsa04310

11. Kharchyshyn V., Melnichenko Yu., Shulko O., Onyshchenko L., Tsekhmistrenko S., Bityutskyy V. (2023). Eco-biotechnology: innovative approaches in poultry production. European scientific congress: IX International Scientific and Practical Conference. Madrid, pp. 10–16.

12. Kühl, M., Sheldahl, L. C., Park, M., Miller, J. R., Moon, R. T. (2000). The Wnt/ Ca^{2+} pathway: a new vertebrate Wnt signaling pathway takes shape. Trends in genetics, 16 (7), pp. 279–283. DOI:10.1016/S0168-9525(00)02028-X

13. Li, L., Peng, X., Qin, Y., Wang, R., Tang, J., Cui, X., Li, B. (2017). Acceleration of bone regeneration by activating Wnt/β-catenin signalling pathway via lithium released from lithium chloride/calcium phosphate cement in osteoporosis. Scientific reports, 7 (1), 45204. DOI:10.1038/srep45204

14. Liu, J., Xiao, Q., Xiao, J., Niu, C., Li, Y., Zhang, X., et al. (2022). Wnt/β-catenin signalling: Function, biological mechanisms, and therapeutic opportunities. Signal. Transduct. Target. Ther. 7, 3 p. DOI:10.1038/s41392-021-00762-6

15. Malik, S., Muhammad, K., Waheed, Y. (2023). Nanotechnology: A revolution in modern industry. Molecules, 28 (2), 661 p. DOI:10.3390/ molecules28020661

16. McQuate, A., Latorre-Esteves, E., Barria, A. (2017). A Wnt/calcium signaling cascade regulates neuronal excitability and trafficking of NMDARs. Cell reports, 21 (1), pp. 60–69. DOI:10.1016/j.celrep.2017.09.023

17. Nakamoto M, Hisaoka M. (2016). Clinicopathological Implications of Wingless/int1 (WNT) Signaling Pathway in Pancreatic Ductal Adenocarcinoma. J UOEH, 38 (1), pp. 1–8. DOI:10.7888/juoeh.38.1

18. Narvaes, R.F., Nachtigall, E.G., Marcondes, L.A., Izquierdo, I., Myskiw, J.D.C., Furini, C.R. (2022). Involvement of medial prefrontal cortex canonical Wnt/β-catenin and non-canonical Wnt/Ca^{2+} signaling pathways in contextual fear memory in male rats. Behavioural Brain Research, 430, 113948. DOI:10.1016/j.bbr.2022.113948

19. Nusse, R., Varmus, H.E. (1982). Many tumors induced by the mouse mammary tumor virus contain a provirus integrated in the same region of the host genome. Cell, 31, pp. 99–109. DOI:10.1016/0092-8674(82)90409-3

20. Rogan, M.R., Patterson, L.L., Wang, J.Y., McBride, J.W. (2019). Bacterial manipulation of Wnt signaling: a host-pathogen tug-of-Wnt. Frontiers in immunology, 10, 2390. DOI:10.3389/fimmu.2019.02390

21. Shah, K., Kazi, J.U. (2022). Phosphorylation-Dependent Regulation of WNT/Beta-Catenin Signaling. Frontiers in Oncology, 12, 858782. DOI:10.3389/fonc.2022.858782

22. Shaker, J.L., Deftos, L. (2018). Calcium and phosphate homeostasis. Endotext [Internet]. Available at:https://www.ncbi.nlm.nih.gov/books/NBK279023/

23. Tripathi, A., Prakash, S. (2022). Nanobiotechnology: Emerging trends, prospects, and challenges. Agricultural Nanobiotechnology, pp. 1–21. DOI:10.1016/B978-0-323-91908-1.00006-7

24. Tsekhmistrenko, S.I., Bityutskyy, V.S., Tsekhmistrenko, O.S., Demchenko, O.A., Tymoshok, N.O., Melnychenko, O.M. (2022). Ecological biotechnologies of "green" synthesis of nanoparticles of metals, metaloxides, metalloids and the iruse. 270 p (in Ukrainian).

25. Tymoshok, N.O., Demchenko, O.A., Bityutskyy, V.S., Tsekhmistrenko, S.I., Kharchuk, M.S., Tsekhmistrenko, O.S. (2023). Bionanotechnology of Selenite Ions Recovery into Nanoselenium by Probiotic Strains of Lactobacteria and Tolerance of Lactobacteria to Sodium Selenite. Microbiologial journal, 85 (4), pp. 9–20. DOI:10.15407/microbiolj85.04.009

26. Wang, B., Wang, S., Ding, M., Lu, H., Wu, H., Li, Y. (2022). Quercetin regulates calcium and phosphorus metabolism through the Wnt signaling pathway in broilers. Frontiers in Veterinary Science, 8, 786519. DOI:10.3389/fvets.2021.786519

27. Wang, D., Ali, F., Liu, H., Cheng, Y., Wu, M., Saleem, M. Z., Peng, J. (2022). Quercetin inhibits angiotensin II-induced vascular smooth muscle cell proliferation and activation of JAK2/STAT3 pathway: A target based networking pharmacology approach. Frontiers in Pharmacology, 13, 1002363. DOI:10.3389/fphar.2022.1002363

28. Xiao, Q., Chen, Z., Jin, X., Mao, R., Chen, Z. (2017). The Many Postures of Noncanonical Wnt Signaling in Development and Diseases. BioMed Pharmacother, 93, pp. 359–369. DOI:10.1016/j.biopha.2017.06.061

29. Zhao, H., Ming, T., Tang, S., Ren, S., Yang, H., Liu, M., Xu, H. (2022). Wnt signaling in colorectal cancer: Pathogenic role and therapeutic target. *Molecular* cancer, 21(1), 144 p. DOI:10.1186/s12943-022-01616-7

Біонанотехнологічні стратегії синтезу кон'югатів кверцетину з наночастинками селену з метою їх націлювання на сигнальний шлях Wnt/Ca^{2+}

Бітюцький В.С., Цехмістренко С.І., Демченко О.А., Цехмістренко О.С., Мельниченко Ю.О., Харчишин В.М.

Одним із застосувань нанотехнологій є синтез наночастинок для цільової доставки ліків та профілактики захворювань. В аграрному секторі нанотехнології мають великі перспективи для покращення здоров'я та продуктивності тварин. У статті розглянуто переваги «зеленого» синтезу наночастинок селену, функціоналізованих флавоноїдом кверцетином, та їх потенціал у профілактиці захворювань кісток у бройлерів. Селен є важливим мікроелементом, який відіграє вирішальну роль у різних фізіологічних процесах, включаючи регуляцію метаболізму кісткової тканини. Його дефіцит може призвести до захворювань кісток, таких як остеопороз та остеомаляція. З іншого боку, було доведено, що кверцетин, природна рослинна сполука, має численні переваги для здоров'я, включаючи протизапальні, антиоксидантні та протиракові властивості. Однак біодоступність і стабільність кверцетину обмежені, що робить його терапевтичний потенціал складним для використання. Щоб подолати ці обмеження, розроблені біонанотехнологічні стратегії синтезу кон'югатів кверцетину з наночастинками селену. Такий підхід не тільки підвищує стабільність та біодоступність кверцетину, але й дозволяє цілеспрямовано доставляти його до певних тканин або клітинних шляхів. Функціоналізація наночастинок Селену флавоноїдом кверцетином сприяє впливу нанокон'югату на транскрипційні фактори Nrf2 та NF-kB, Wnt ключові шляхи, які регулюють тонкий баланс клітинного окисно-відновного статусу та реакції на стрес і запалення, метаболізм Кальцію та Фосфору. У цьому випадку мішенню є сигнальний шлях Wnt - складний каскад процесів, що беруть участь у метаболізмі кісткової тканини. Встановлено, що синтезовані біокон'югати наноселен-кверцетин модулюють сигнальний шлях Wnt різними способами. По-перше, вони знижують активність білка β-катеніну, ключового регулятора сигнального шляху Wnt, сприяють підтриманню балансу між формуванням та резорбцією кісткової тканини, запобігаючи таким чином захворюванням кісток. По-друге, ці біокон'югати підвищують активність білка LRP6, рецептора Wnt, що ще більше посилює ефективність сигнального шляху. Нарешті, вони впливають на експресію генів, активованих сигнальним шляхом Wnt, таким чином регулюючи метаболізм кальцію та фосфору, важливих елементів для здоров'я кісток. Потенціал цих біонанотехнологічних стратегій величезний, особливо в сільськогосподарському секторі. Запобігаючи захворюванням кісток у бройлерів, можна значно підвищити профілактику захворювань та продуктивність птиці. Використання досягнень нанотехнологій може слугувати екологічною альтернативою використання антибіотиків та інших фармацевтичних препаратів, сприяючи загальному здоров'ю і благополуччю тварин. Таким чином, «зелений» синтез наночастинок селену, функціоналізованих кверцетином, пропонує перспективне рішення для таргетування сигнального шляху Wnt, регулювання метаболізму кальцію і фосфору та профілактики захворювань кісток у бройлерів. Цей біонанотехнологічний підхід не лише покращує стабільність та біодоступність кверцетину, й посилює його терапевтичний потенціал. Використовуючи потенціал нанотехнологій в аграрному секторі, ми можемо покращити здоров'я тварин, знизити рівень захворюваності та підвищити продуктивність, що в кінцевому підсумку принесе користь як тваринам, так і людям.

Ключові слова: біонанотехнологія, «зелений» синтез, фактор Nrf2, NF-kB, Wnt, β-катенін, Селен, Кальцій, Фосфор. «green»

ORCID iD:
Bityutskyy V. https://orcid.org/0000-0002-2699-3974
Tsekhmistrenko S. https://orcid.org/0000-0002-7813-6798
Demchenko O. https://orcid.org/0000-0003-1457-143X
Tsekhmistrenko O. https://orcid.org/0000-0003-0509-4627
Melnychenko Yu. https://orcid.org/0000-0002-1324-0762
Kharchyshyn V. https://orcid.org/0000-0002-3403-3535